Pilot Study: Investigating a Novel Supplement-based Therapy for the Treatment of Small Intestinal Bacterial Overgrowth

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Study Synopsis

The aim of this pilot study is to determine the efficacy of a supplement protocol combined with a low FODMAP diet for the treatment of small intestinal bacterial overgrowth (SIBO). The study is designed as a prospective, open label investigation, with an estimated sample size of 10 patients.

Patients diagnosed with SIBO by Dr. Nathan Morris at Good Medicine Clinic (Oxford, Ohio) will be offered the opportunity to enroll in this study, if they satisfy the inclusion and exclusion criteria upon initial diagnosis. No control group will be assigned.

The diagnosis of SIBO will be determined via assessment of clinical symptoms and the results of a lactulose breath test. This diagnosis procedure is, currently, the standard-of-care. After administration of the supplement therapy and adherence to a low FODMAP diet (8 weeks), the lactulose breath test will be repeated and symptoms re-assessed by Dr. Morris.

The post-treatment lactulose breath test and all supplements in the protocol will be provide free-of-charge to enrolled patients. In addition, enrolled patients will not be billed for the mid-treatment office visit. Patient and/or patient insurance will be responsible for all other expenses, including but not limited to the initial breath test, all other office visits and travel.

Background

Small intestinal bacterial overgrowth (SIBO) is a category of gastrointestinal infection, characterized by an increased concentration (>100,000 CFU/mL proximal jejunal fluid) of bacteria in the small intestine.¹ Symptoms of SIBO commonly afflict the gastrointestinal tract and include but are not limited to: abdominal pain, discomfort, bloating, cramping, flatulence, diarrhea, constipation, eructation, and low serum B12.³,4

SIBO is believed to be severely under diagnosed and is associated with numerous comorbid conditions including irritable bowel syndrome, diabetes mellitus and hypothyroidism.^{4,5} Small-bowel aspiration (SBA) or breath tests are used to aid in the diagnosis of SIBO. Due to the cost and invasive nature of SBA, glucose or lactulose breath tests are more commonly performed.

The treatment of SIBO frequently consists of antibiotic therapy. Rifaxamin is a poorly absorbed antibiotic with bacteriocidal activity against enteropathogens and is widely prescribed for the treatment of SIBO.³ Nevertheless, both patients and practitioners frequently turn to complementary and alternative medicine, due to the adverse effects associated with antibiotic use and the recurrent nature of SIBO. In 2014, a retrospective study (Chedid et al.) found that the efficacy of a particular herbal therapy was comparable to Rifaxamin treatment.³ However, both treatment

options demonstrated a response rate of less than 50%. This investigation will test a more comprehensive, supplement-based therapy in hopes of achieving a greater response rate.

Objectives

This investigation aims to determine the efficacy of a supplement protocol in combination with a low FODMAP diet for the treatment of small intestinal bacterial overgrowth (SIBO).

Patient Selection

Patients diagnosed with SIBO at Dr. Morris' clinic will be offered the opportunity to enroll in this study as a theoretical treatment option for SIBO. Other treatment options will be discussed with the patient. Enrolled patients must satisfy the following inclusion and exclusion criteria:

Inclusion criteria: A positive diagnosis of SIBO, which will be defined by 1) presentation of the aforementioned symptoms and 2) positive results of a lactulose breast test. Positive breath test results will be defined as an increase in hydrogen of 20 ppm or more and/or an increase in methane of 12 ppm or more compared to baseline by 90 minutes.

Exclusion criteria: 1) Use of prescription antibiotics or antifungals within the past 4 weeks. 2) Younger than 18 or older than 85 years of age 3) Pregnant or breast-feeding 4) Major drug-supplement interactions between essential medication and the proposed supplement therapy. 5) A known allergy to one or more of the ingredients in the supplement therapy. 6) Has been diagnosed and treated for SIBO within the past 6 months. 7) Has undergone a colonoscopy or barium enema within the past 4 weeks. 8) Has an allergy to lactulose. 9) Has diabetes mellitus.

Study Procedures

The supplement protocol is designed to take 8 weeks. Due to the delay in receiving and interpreting test results, the investigation, in its entirety, is estimated to take 12 weeks.

- Visit -1 Dr. Morris will assess patient history and symptoms, at his facility in Oxford, Ohio. If suggestive of SIBO, a lactulose breath test will be prescribed. Additional testing may be performed, at the discretion of Dr. Morris, to aid in the initial diagnosis of the patient.
- Visit 0 Dr. Morris will assess the results of the breath test and confirm or deny the diagnosis of SIBO. Treatment options for SIBO will be discussed, and the patient will be made aware of this investigation as a theoretical treatment option. Patient eligibility will be determined by Dr. Morris who will complete the Patient Eligibility Checklist (Appendix A) for each patient. All female patients will be asked to complete a urine pregnancy test to confirm pregnancy status. Eligible patients will be asked to review

and sign the Informed Consent document. Carman Clark (Medical Assistant at Good Medicine) will be available to discuss patient consent and confidentiality. Enrolled patients will be asked to complete a baseline Medical Symptom Questionnaire (Appendix B). Afterwards, Ms. Clark will review the supplement therapy (Supplement Overview - Appendix C) and low FODMAP diet (Low FODMAP Handout - Appendix D). Patients will then be provided with all supplements necessary to complete the investigation. Patients will be asked to discontinue all other supplements during the study. However, no wash out period is required. Prescription medications, over-the-counter medications and/or supplements deemed medically necessary by the patient's primary care physician and/or Dr. Morris may be continued, if there are no known contraindications.

- Visit 1 will occur approximately 4 weeks after the patient begins the supplement protocol. Patients will be asked to report their compliancy with the supplement protocol and low FODMAP diet and describe adverse effects. Patients will also be asked to complete the Medical Symptom Questionnaire. Patients will be provided with the second lactulose breath test kit and instructed to perform the test within 2 weeks of completing the supplement therapy.
- Visit 2 will occur after the results of the post-treatment breath test are available. Dr. Morris will interpret the results of the second breath test, and patients will be asked to complete the Medical Symptom Questionnaire, report compliancy with the supplement protocol and low FODMAP diet, and describe any adverse effects. Further treatment options will be discussed if necessary; follow-up treatment will be outside the scope of this investigation.

Risk/Safety Information

This study presents risk in the form of adverse reactions to ingredients in the supplement therapy. Patient risk will be minimized by excluding patients who may respond poorly to the supplement therapy or testing procedures from the study, i.e., by abiding by the aforementioned patient enrollment exclusion criteria.

Monitoring/Reporting

Patients may report adverse events to Good Medicine during scheduled office visits or by phone during office hours. If serious or life-threatening side effects arise, patients are instructed to call 911. Possible side effects include but are not limited to: diarrhea, constipation, nausea, vomiting, bloating or headache. When necessary, Dr. Morris or Ms. Clark will communicate with patients outside the office by phone and record adverse events in the patient's confidential files. Medical guidance will be provided as necessary.

This study will be terminated if one-half or more of enrolled patients withdraw due to adverse events. Dr. Morris and Dr. Kelly Heim (Senior Director, Scientific Affairs at Atrium Innovations) will monitor, determine the need for and facilitate the termination of the study. Direct access to study related data will be made available for monitoring, auditing, IRB review and regulatory inspection.

Data Management

Lactulose breath test scores and completed Medical Symptom Questionnaire will be compared pre- and post-treatment to determine the efficacy of the supplement therapy. The significance of the change in breath test scores will be determined if the final sample size permits such analysis.

IRB Review/Ethics/Informed Consent

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

Any changes to the protocol will be submitted to the IRB for review and approval before implementation. However, a protocol change intended to eliminate an apparent immediate hazard to patients will be implemented immediately. The reviewing IRB will be notified within 10 working days, if an immediate protocol change is necessitated.

The principle investigator (Dr. Nathan Morris) will provide each patient with full and adequate verbal and written information using the IRB approved informed consent documentation, including the objective and procedures of the study as well as the possible risks involved before inclusion in the study. Informed consent will be obtained prior to performing any study-related procedures, including screening and changes in medications including any washout of medications. A copy of the signed informed consent will be given to the study patient.

Confidentiality

Study-related records identifying the patient will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available. The IRB and/or other regulatory authorities will have access to study related medical records upon request. Subsequent use of the collected data will exclude patient identifying information.

Intended Use of the Data

The data collected from this investigation will be used to determine the efficacy of the proposed supplement therapy. If efficacious, the results will be distributed in print and digital advertising.

References

- 1. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010;16(24):2978-90.
- 2. Ford AC, Spiegel BM, Talley NK, Moayyedi P. Small Intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta analysis. Clin Gastroenterol Hepatol. 2009;7(12):1279-86
- 3. Chedid V, Dhalla S, Clarke J, et al. Herbal Therapy is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth. Global Advances in Health and Medicine Journal. 2014; 3(3): 16-22.
- 4. Reynolds K. Small Intestinal Bacterial Overgrowth: A Case-Based Review. Journal of Patient-Centered Research and Reviews. 2015; 2(4): 165-171.
- 5. Saad R and Chey W. Breath Testing for Small Intestinal Bacterial Overgrowth: Maximizing Test Accuracy. Perspectives in Clinical Gastroeneterology and Hepatology. 2014; 12:1964-1972.

Appendix A

Patient Eligibility Checklist

This documented is to be complete by Dr. Nathan Morris.

YES / NO Patient is am between the ages of 18 and 85 years old.

YES / NO Patient has used oral, prescription antibiotics and/or antifungals within the

past 12 weeks.

YES / NO Patient is pregnant or breast-feeding or plans to become pregnant/breast-

feeding within the next 4 months.

YES / NO Patient is currently taking one or more of the following medications.

Amiodarone (Cordarone, etc.) Estrogen replacement therapy Anti-diabetes medications Etoposide (Etopophos, etc.)

Artemether (Artenam, etc) Halofantrine

Atorvastatin (Lipitor) Intravenous nitroglycerin Benzodiazepines Lovastatin (Mevacor, etc.)

Buspirone (BuSpar) Lactulose

Calcium channel blockers Methylprednisolone (Medrol, etc.)

Carbamazepine (Tegretol, etc) Pravastatin (Pravachol)
Carvedilol (Coreg) Praziquantel (Biltricide)

Cisapride (Propulsid) Quinidine Clomipramine (Anafranil) Scopolamine

Cyclosporine (Neoral, etc)

Dextromethorphan (Robitussin, etc

etc)

Sildenafil (Viagra, etc.)

Simvastatin (Zocor)

Terfenadine (Seldane)

	Alpha lipoic acid	L-methionine
	Artichoke	Milk thistle
	Berberine	N-acetyl-l-cysteine
	Broccoli	Olive
	Chlorella	Pineapple
	Clove	Safflower
	Coconut	Sunflower
	Glycine	Sweet wormwood
	Grapefruit	Taurine
	Kiwi	Thistle
		Turmeric
	L-glutamine	rurmeric
YES / NO	Patient has a history of o	ne or more of the following conditions.
	Bile duct obstruction	
	Immunodeficiency	
	Kidney stones	
	Peptic ulcers	
	reptic dicers	
YES / NO	Patient has have been dimonths.	agnosed and treated for SIBO within the past 6
YES / NO	Patient has undergone a weeks	colonoscopy or barium enama within the past 4
YES / NO	Patient has diabetes mel	litus.
Patient Nan	ne (Print)	
Data		
Date		
Dr. Nathan	Morris (Sign)	

Patient has a known allergy to one or more of the following ingredients.

YES / NO

Appendix B

The MSQ will be administered online via the Living Matrix platform. The following is a print copy of the questionnaire. Instructions to access the Living Matrix will also be provided to patients. This document was submitted to Schulman as an additional file.

Living Matrix MSQ

Please answer EVERY QUESTION in this section. Select "Zero" if you do not have this symptom.

	Rate the Syn	nptom
Headache	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Faintness	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Dizziness	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Insomnia	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Eyes		

	Rate the Symptom
Watery or itchy eyes	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Swollen, red or sticky eyelids	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Bags or dark circles under eyes Blurred or tunnel vision-does not include near or far- sightedness	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Ears	
Rate the Symptom	
O - Never or almost never 1 - Occasionally have it, of 2 - Occasionally have it, of 3 - Frequently have it, effective of the series of the ser	effect is not severe effect is severe Cect is not severe

Earaches	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Ear infections	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Drainage from ear	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Ringing in ears	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O - Never or almost never have the symptom O
Hearing loss	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Frequently have it, effect is not severe C - Frequently have it, effect is severe

Nose

Rate the Symptom

Stuffy nose	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Sinus problems	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Hay fever	. 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Sneezing attacks	. 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe

Excessive mucus formation

Mouth/Throat

Rate the Symptom		
Chronic coughing	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 	
	• 2 - Occasionally have it, effect is severe	

Rate the Symptom 0 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 0 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Gagging 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 0 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Frequent throat clearing 0 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe Sore throat 0 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe hoarseness 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 0 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Loss of voice 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe -0 Swollen or discolored tongue, gums or lips 0 - Never or almost never have the symptom

	•	0	1 - Occasionally have it, effect is not severe
	•	0	2 - Occasionally have it, effect is severe
	•	0	3 - Frequently have it, effect is not severe
	•	0	4- Frequently have it, effect is severe
	•	0	0 - Never or almost never have the symptom
	•	_	1 - Occasionally have it, effect is not severe
Canker sores	•	0	2 - Occasionally have it, effect is severe
	•	0	3 - Frequently have it, effect is not severe
	•	0	4- Frequently have it, effect is severe

Skin

	Rate the Sym	nptom
Acne	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Hives or Urticaria	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Rashes	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe

Dry skin	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Hair loss	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Flushing	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Hot flashes	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Excessive sweating	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe

Heart

Rate the Symptom 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe Irregular or skipped heartbeat 2 - Occasionally have it, effect is severe 0 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Rapid or pounding heartbeat \circ 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe $\boldsymbol{0}$ - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe Chest pain 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe Lungs

Chest congestion		 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Asthma •	. 0	0 - Never or almost never have the symptom1 - Occasionally have it, effect is not severe2 - Occasionally have it, effect is severe

	•	0	3 - Frequently have it, effect is not severe
	•	0	4- Frequently have it, effect is severe
	•	0 0 0	0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe
Bronchitis	•	0	2 - Occasionally have it, effect is severe3 - Frequently have it, effect is not severe
	•	0	4- Frequently have it, effect is severe
Shortness of breath	•	0000	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe
	•	\circ	4- Frequently have it, effect is severe
	•	0	0 - Never or almost never have the symptom1 - Occasionally have it, effect is not severe
Difficulty breathing	•	0	2 - Occasionally have it, effect is severe
	•	0	3 - Frequently have it, effect is not severe
	•	0	4- Frequently have it, effect is severe

Digestive Tract

	v	•
Nausea or Vomiting	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Diarrhea	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Constipation	. 0	0 - Never or almost never have the symptom

Rate the Symptom

1 - Occasionally have it, effect is not severe

•	0	2 - Occasionally have it, effect is severe3 - Frequently have it, effect is not severe4- Frequently have it, effect is severe
Bloated feeling	•	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Belching	•	O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Passing gas	•	O - Never or almost never have the symptom O 1 - Occasionally have it, effect is not severe O 2 - Occasionally have it, effect is severe O 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Heartburn	•	O - Never or almost never have the symptom I - Occasionally have it, effect is not severe C - Occasionally have it, effect is severe C - 3 - Frequently have it, effect is not severe C - 4- Frequently have it, effect is severe
Intestinal or stomach pain	•	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe

•	3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Joints/Muscle Rate the Symptom Pain or aches in joints	 O - Never or almost never have the symptom O 1 - Occasionally have it, effect is not severe O 2 - Occasionally have it, effect is severe O 3 - Frequently have it, effect is not severe O 4- Frequently have it, effect is severe
Arthritis	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Stiffness or limitation of movement	 O - Never or almost never have the symptom O 1 - Occasionally have it, effect is not severe O 2 - Occasionally have it, effect is severe O 3 - Frequently have it, effect is not severe C 4- Frequently have it, effect is severe
Pain or aches in muscles	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Feeling of weakness or tiredness	 O - Never or almost never have the symptom O 1 - Occasionally have it, effect is not severe O 2 - Occasionally have it, effect is severe O 3 - Frequently have it, effect is not severe O 4- Frequently have it, effect is severe

• 2 - Occasionally have it, effect is severe

Weight

Craving certain foods	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Excessive weight	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Compulsive eating	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Water retention	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Underweight	. 0 . 0 . 0 . 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe

Energy/Activity

Fatigue	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Sluggishness	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe
Apathy	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Lethargy	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe
Hyperactivity	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Restlessness	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe

- 2 Occasionally have it, effect is severe
- 3 Frequently have it, effect is not severe
- 4- Frequently have it, effect is severe

Mind

	Rate the Symptom
Poor memory	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Confusion	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe
Poor comprehension	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe
Poor concentration	 O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Never or almost never have the symptom O - Never or almost never have the symptom O - Occasionally have it, effect is not severe O - Occasionally have it, effect is not severe O - Occasionally have it, effect is severe O - Occasionally have it, effect is severe
Poor physical coordination	 O - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe

	. 0	3 - Frequently have it, effect is not severe4- Frequently have it, effect is severe
Difficulty in making decisions	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Stuttering or stammering	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Slurred speech	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe
Learning disabilities	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe

Emotions

Rate the Symptom

O - Never or almost never have the symptom
 O - Occasionally have it, effect is not severe
 O - Occasionally have it, effect is severe
 O - Never or almost never have the symptom
 O - Occasionally have it, effect is not severe
 O - Never or almost never have the symptom
 O - Frequently have it, effect is not severe

Rate the Symptom				
Anxiety	. © 0 . © 1 . © 2 . © 3	- Never or almost never have the symptom - Occasionally have it, effect is not severe - Occasionally have it, effect is severe - Frequently have it, effect is not severe - Frequently have it, effect is severe		
Fear	. O 1 . O 2 . O 3	 Never or almost never have the symptom Occasionally have it, effect is not severe Occasionally have it, effect is severe Frequently have it, effect is not severe Frequently have it, effect is severe 		
Nervousness	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 		
Anger	. 0	 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 2 - Occasionally have it, effect is severe 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 		
	. 0	0 - Never or almost never have the symptom		

Irritability

1 - Occasionally have it, effect is not severe
 2 - Occasionally have it, effect is severe

3 - Frequently have it, effect is not severe4- Frequently have it, effect is severe

Aggressiveness	. 0	0 - Never or almost never have the symptom
	. 0	1 - Occasionally have it, effect is not severe
	. 0	2 - Occasionally have it, effect is severe
	. 0	3 - Frequently have it, effect is not severe
	. 0	4- Frequently have it, effect is severe
Depression	. 0	0 - Never or almost never have the symptom
	. 0	1 - Occasionally have it, effect is not severe
	. 0	2 - Occasionally have it, effect is severe
	. 0	3 - Frequently have it, effect is not severe
	. 0	4- Frequently have it, effect is severe

0 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe Frequent illness 2 - Occasionally have it, effect is severe 0 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Frequent or urgent urination 0 3 - Frequently have it, effect is not severe 4- Frequently have it, effect is severe 0 0 - Never or almost never have the symptom 1 - Occasionally have it, effect is not severe 0 2 - Occasionally have it, effect is severe Genital itch or discharge

0

0

3 - Frequently have it, effect is not severe

4- Frequently have it, effect is severe

Appendix C

Small Intestinal Bacterial Overgrowth (SIBO) Protocol

Dietary Recommendations

Follow the low FODMAP diet at the guidance of a healthcare professional. See included Stanford University Medical Center FODMAP handout for a brief introduction to this diet.

Duration

This protocol is designed to take 8 weeks.

Product Overview

Category	Products	Servings per Bottle	Capsules per Day	Duration	Number of Bottles*
Detox Support	Liver-G.I. Detox	60 capsules	2 per day	30 days	One bottle
GI Support	L-Glutamine Powder	73 scoops	2 scoops per day	35 days	One bottle
Microbial Balance	MicroDefense	90 capsules	1 per day	49 days	One bottle
Microbial Balance	A.C. Formula II	120 capsules	4 per day	49 days	Two bottles
Probiotic	Probiotic-5	60 capsules	1 per day	49 days	One Bottle
Digestive Enzymes	Digestive Enzymes Ultra with Betaine HCI**	180 capsules	As needed (up to 6)	Long term	One bottle

^{*}The number of capsules purchased may exceed the amount required by this protocol, due to limited bottle sizes.

^{**}Digestive Enzymes Ultra with Betaine HCl may be replaced with Digestive Enzymes Ultra, if patient responds poorly to Betaine HCl.

Protocol

	Product	Breakfast	Lunch	Dinner
	Liver-G.I. Detox	1 capsule		1 capsule
Week 1	Digestive Enzymes Ultra with Betaine	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal
	Liver-G.I. Detox (finish 2 days into week 5)	1 capsule		1 capsule
	Digestive Enzymes Ultra with Betaine	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal
Weeks	L-Glutamine	1 serving	1 serving	
2 – 5	A.C. Formula II	2 capsules before meal	2 capsules before meal	
	MicroDefense		1 capsule before meal	
	Probiotic-5			1 capsule
	Digestive Enzymes Ultra with Betaine	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal
	L-Glutamine	1 serving	1 serving	
Week 6	A.C. Formula II	2 capsules before meal	2 capsules before meal	
	MicroDefense		1 capsule before meal	
	Probiotic-5			1 capsule
	Digestive Enzymes Ultra with Betaine	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal	1-2 capsules or as needed before meal
Weeks	A.C. Formula II	2 capsules before meal	2 capsules before meal	
7 & 8	MicroDefense		1 capsule before meal	
	Probiotic-5			1 capsule



Low-FODMAP Food Plan



☐ Oils, salad: Almond,

virgin), safflower

☐ Olives: Black, green,

 \square Pesto (olive oil)-1 t

walnut-1 t

Kalamata-8

avocado, flaxseed oil,

(high-oleic), sesame,

sunflower (high-oleic),

hempseed, olive (extra

PROTEINS

Proteins

DAIRY & ALTERNATIVES Proteins/Carbs

FATS & OILS

Fats

Lean, free-range, grass-fed, organically grown animal
protein; non-GMO, organic plant protein; and wild-
caught, low-mercury fish preferred. Canned meats are
allowed if cans are BPA-free and if the meat is free of
high-FODMAP fillers.

nign-FODIVIAP fillers.	
Animal Protein: □ Cheese (hard): cheddar, colby, feta, havarti, manchego, Pecorino, Swiss-½ oz □ Cheese (soft): brie, Camambert, chevre, goat cheese,	 □ Meat: beef, buffalo, elk, lamb, pork, venison, other wild game-1 oz □ Poultry (skinless): Chicken, Cornish hen, duck, pheasant, turkey, etc1 oz Plant Protein:
mozzarella–1 oz Cottage cheese (dry curd)–½ c Cream cheese–2 T Parmesan cheese–2 T Ricotta cheese–2 T Egg–1, or 2 egg whites Fish/shellfish: Anchovies, clams, cod, flounder, halibut, salmon, sardines, trout, tuna, etc.–1 oz	Spirulina−2 T □ Tempeh−1 oz □ Tofu (firm/extra firm)−1½-2 oz Protein Powder: □ Check label for # grams/scoop (1 protein serving=7 g) Bovine collagen, egg, hemp, whey protein isolate
1 serving as listed = 35-75 calorie	es, 5–7 g protein, 3–5 g fat,

0-4 g carbs

Average protein serving is 3-4 oz (size of palm of hand).

LEGUMES

Proteins/Carbs

Organic, non-GMO preferred

☐ Black beans	□ Chickpeas
(canned only) $-\frac{1}{4}c$	(canned only) $-\frac{1}{4}c$
☐ Green peas	☐ Hummus−1 T
$(cooked)$ - $\frac{1}{8}c$	☐ Mung beans
	(cooked)-1/4 c

1 serving = 90-110 calories, 3-7 g protein, 0 fat, 15 g carbs

J	Insweet	lened.	organic	pref	errec
ì	1131100	oncu,	oigaine	Pici	01100

Do	ıiry:
	Milk (plain): Lactose-
	free cow, goat-8 oz
	Yogurt (plain): Lactose
	free cow, goat-4-6 oz

Dairy Alternatives: ☐ Milk: Almond, hemp—

8 oz ☐ Milk: Coconut-4 oz ☐ Milk: Rice-6 oz ☐ Yogurt (plain): coconut-4-6 oz

1 dairy serving = 90-150 calories, 7-8 g protein, 12 g carbs 1 dairy alternative serving = 25-90 calories, 1-9 g protein, 1-4 g carbs (nutritional values vary)

Buttermilk, evaporated milk, goat milk, heavy cream, kefir, oat milk, sour cream, soy milk, sweetened condensed milk, yogurt (except those listed), and any other lactose-containing dairy products. Check milk substitutes for high-FODMAP sweeteners and additives. Unsweetened homemade dairy alternatives are preferred.

NUTS & SEEDS

(sesame seed) $-\frac{1}{2}$ T

1 serving = 45 calories, 5 g fat

Eliminate Cashews and pistachios. Proteins/Fats

Unsweetened, unsalted, organic preferred			
	Almonds-6		Nut flour/meal:
	Brazil nuts-2		Almond $-\frac{1}{4}$ c
	Chia seeds-1 T		Peanuts-10
	Chestnuts-5		Pecan halves-4
	Coconut (fresh)-1/3 c		Pine nuts–1 T
	Coconut (dried,		Pumpkin seeds-1 T
	shredded)-3 T		Sesame seeds $-1\ T$
	Flax seeds-½ T		Sunflower seeds– $1/2$ T
	Hazelnuts-5		Walnut halves-4
	Macadamias-2-3		
	Nut and seed butters:		
	Almond, tahini		

Minimally refined, cold pressed, organic, non-GMO preferred

 o protection
Avocado-2 T or
1/8 whole
Butter/ghee (clarified
butter, grass-fed)–1 t
Coconut milk, regular
(canned)-1 ½ T
Coconut milk, light
(canned)-3 T
Mayonnaise
(unsweetened) $-1 t$
Oils, cooking: Avocado,
coconut, ghee, olive

(extra virgin), rice bran, sesame-1 t 1 serving = 45 calories, 5 g fat

Eliminate

Chocolate, soybean oil, and any salad dressings or sauces made with sweeteners or other high-FODMAP additives.

Items in orange indicate moderate- and high-FODMAP foods that may be tolerated in reduced serving sizes, as specified. Limit orange foods to a maximum 1 serving from each food category daily.

Notes: Nutritional amounts are based on average values for the variety of foods within each food category.

> Dietary prescription is subject to the discretion of the health practitioner.



VEGETABLES Non-star	chy C arbs	FRUITS	C arbs	BEVERAGES, SPICES	& CONDIMENTS
Artichoke hearts (canned)—1/8 c Arugula Asparagus—1 spear Bamboo shoots Beets (cubed)—1/4 c Bok choy Broccoli—1/4 c Cabbage: Green, purple, Savoy Carrots Celeriac root Celery—1/4 med stalk Chard/Swiss chard Chervil Chives Cilantro Cucumbers Daikon radishes Eggplant Endive Escarole	Horseradish Kohlrabi Lettuce, all Microgreens Parsley Parsnips Peppers, all Pumpkin (canned only)-¼ c Radicchio Radishes Scallions (green part only)-2 T Sea vegetables Snow peas-5 pods Spinach Sprouts: Alfalfa, bean Squash: Delicata, chayote, spaghetti, yellow, zucchini Tomato Tomato Tomato juice-¾ c	Unsweetened, no sugar ad Banana—½ med Blueberries—¾ c Cranberries, currants, Gogi berries, papaya, pineapple, raisins—1 T Grapefruit—½ med Grapes—15 Guava—1 med Kiwi—1 med Melon, all—1 c 1 serving = 60 calories, 15 g carte Eliminate Apples, applesauce, apricots, blackbifgs, lychee, mango, nectarines, peacwatermelon, and all canned fruit.	ded ☐ Orange—1 sm ☐ Papaya—1 c ☐ Passionfruit—1 med ☐ Pineapple—¾ c ☐ Pomegranate seeds—¼ c ☐ Raspberries—1 c ☐ Rhubarb—1 c ☐ Starfruit—1 med ☐ Strawberries—1½ c ☐ Tangerines—2 sm Deserties, boysenberries, cherries, dates, pears, persimmon, plums, prunes,	□ Filtered water □ Sparkling/mineral water □ Coconut water-4 oz □ Coffee □ Fruit juice: Orange, cranberry-4 oz □ Tea: Black, chai green, peppermint, white □ Tea (diluted): Chamomile, herbal, oolong □ Cacao powder □ Cocoa powder □ Herbs: basil, cilantro, curry leaves, kafir lime, lemongrass, mint, parsley, rosemary, sage, tarragon, thyme, watercress Approved sweeteners: Maple sy use sparingly, suggest 1 t.	☐ Spices, all ☐ Condiments: Fish sauce, ketchup (unsweetened), lemonalime juice, miso paste, mustard, vinegar (apple cider, balsamic , rice wine), Worchestershire sauce—use sparingly, suggest 1 T or less per serving
☐ Fennel ☐ Fermented vegetables: Kimchi, sauerkraut—1 T ☐ Green beans ☐ Greens: Beet, collard, kale, mustard, turnip, etc. ☐ Ginger root—1 t 1 serving = ½ c, 1 c raw greens = Eliminate Bittermelon, Brussels sprouts, cauliflower, leeks, mushrooms, okra, onion, shallots, st. (Jersulaem artichokes), and sweet corn.	☐ Tomato paste, sauce (unsweetened) ☐ Turnips ☐ Vegetable juice—¾ с ☐ Water chestnuts ☐ Watercress 25 calories, 5 g carbs dandelion greens, garlic, jicama, ugar snap peas, sunchokes	Unsweetened, organic pref Gluten Free: Amaranth-1/4 c Buckwheat-1/2 c Cereal: Corn, quinoa-1/2 c Cous cous: Corn, rice-1/4 c Flours: Buckwheat, corn, cornstarch, millet, quinoa, rice, teff, potato, tapioca	☐ Quinoa-½ c ☐ Popcorn-1 c ☐ Rice: Basmati, black, brown, purple, red, white, wild-½ c ☐ Sorghum-½ c ☐ Teff-¾ c Gluten Containing: ☐ Bulgur-¼ c ☐ Spelt-¼ c Individual portions:	Eliminate Artificial sweeteners, dandelion tea, fi garlic salt, honey, and onion salt. Items in orange indicate r FODMAP foods that may b	noderate- and high-
VEGETABLES Starchy □ Acorn squash (cubed)-1 c	□ Potato: Purple, red, sweet, yellow-½ med	 □ Grits: corn (polenta)-½ c □ Millet-½ c □ Oats: quick (rolled)-¼ c □ Oats: steel-cut-½ c 	☐ Bread—1 slice ☐ Pasta—1/3 c ☐ Tortilla—1, 6 in All grain servings are for cooked amounts.	serving sizes, as specified maximum 1 serving from a Notes: Nutritional amounts are be variety of foods within each	Limit orange foods to a each food category daily. assed on average values for the
□ Butternut squash (cubed)—½ c □ Plantain—½ c or ½ whole 1 serving = 80 calories, 15 g carb	☐ Potatoes (mashed)—½ c ☐ Root vegetables: Parsnip, rutabaga, taro, turnip—½ c ☐ Yam—½ med	1 serving = 75–110 calories, 15 g Eliminate Eliminate any breads, cereals, cracker and barley. This includes cous cous (w mixes, naan, Roti, sprouted bread.	rs, pastas, etc., made from wheat, rye,	Dietary prescription is sub health practitioner.	iject to the discretion of the